Impact of guidelines implemented in a Paris university hospital: application to the use of antiemetics by cancer patients

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Aims To assess the impact with time of guidelines on antiemetic use in an 850-bed Paris university hospital with a high proportion of cancer patients.

Methods Guidelines on the use of antiemetics available in cancer chemotherapy were drafted according to the Delphi technique. Their implementation was based upon a patient-specific antiemetic prescription form. To assess the impact of guideline implementation over time, discrepancies between current practice and the guidelines were compared before guideline implementation (between March and August 1995) and after implementation (between March and August 1997, and March and August 1998).

Results Before the Delphi panel's guidelines were implemented, 5-HT₃ antagonists were inappropriately administered in 70% of cases. After guideline implementation, this proportion dropped significantly ($P < 0.0001$, Fisher's exact test) to 22% between March and August 1997 and 28% between March and August 1998.

Conclusions Implementation of guidelines seems to have resulted in significant changes with time, although a causal relationship has not been demonstrated. The development of guidelines by our hospital's multidisciplinary working group helped the various consultants to adjust medical practices to take account of these changes.

Keywords: antiemetics, Delphi technique, drug utilization review, impact of guidelines

Introduction

Guidelines for clinical practice are being promoted as a way of helping practitioners to reach clinical decisions, and of improving the effectiveness and reducing unnecessary costs of health care. However, despite increasing enthusiasm for such guidelines, there is limited evidence that they have any lasting impact on clinical practice. Their success depends on several factors, including the methods of their elaboration, dissemination and implementation. Once the guidelines have been worked out and implemented, the question is to ascertain whether or not they are having the impact expected. It is therefore important to carry out studies to determine whether the guidelines actually reach the physicians for whom they are intended.

In 1994, the most costly drugs in the pharmacy of our

Paris University Hospital (Hôpital Tenon, 850 beds) were 5-HT₃ receptor antagonists. In France, approval of 5-HT₃ receptor antagonists is not restricted with regard to the indications for use, which are defined as the 'preventive and curative treatment of chemotherapy-induced nausea and vomiting'.

In January 1995, the oncologists decided to standardize the antiemetic regimens prescribed in the Tenon Hospital. Radiotherapists and respiratory physicians were also prescribers of chemotherapy in our hospital, and together with the oncologists, constituted a Working Group. These senior clinicians agreed to approve recommendations based on the opinions of a panel of outside experts, according to the Delphi technique, and to participate in an antiemetic utilization study, to be conducted both before and after the implementation of guidelines for this purpose.

The aim of this study was to describe the way in which the following objectives can be achieved: the elaboration, dissemination and implementation of guidelines, and the impact of their implementation over time.

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Methods

The process developed by the Tenon Working Group included three stages: the drafting of guidelines based on experts' recommendations resulting from the Delphi Technique, implementation of the guidelines, and assessment of their impact.

*The Delphi technique**

The Delphi technique was adopted by the Tenon Working Group in order to reach a consensus of opinion on recommendations for treating acute chemotherapy-induced nausea and vomiting. Seven oncologists, three radiotherapists, three respiratory physicians and one hospital pharmacist constituted the group of experts. They were chosen by the Tenon Working Group because they were highly qualified and experienced specialists working outside the Tenon Hospital.

The 14 experts agreed to answer questions anonymously, in writing. After the first round of questions, the Tenon Working Group sent each expert a summary of the opinions expressed by the members of the Delphi group without identifying any of them. In the light of this additional information, the experts were asked to reiterate their opinions.

This process was repeated twice (three rounds in all). One expert failed to answer the second round of questions, and another did not respond at all. After the second and third rounds, as after the first round, the Tenon Working Group circulated the Delphi experts with a summary of the issues considered and the views expressed, and also of their comments. It was hoped that opinions would converge after the 3 rounds of consultation and that a consensus would be reached. In any case, the Working Group agreed that the opinions expressed in the third round would constitute the guidelines on 5-HT₃ antagonist prescription.

*Briefly, this is a method of obtaining answers to questions regarding issues that are uncertain, even to experts; it has three cardinal features: anonymity (no member of the group knows either who the others are, or the views expressed by any of them on a particular question), reiteration (the round of questions is repeated three times), and feed-back (this consists of the inclusion of additional information in each round, in the form of statistics regarding the earlier answers of the group, and the experts' comments). The questions, may be the same in each round, or consist of new queries raised by earlier answers [1–4]. Feed-back and reiteration comprise a sequence of rounds, between which a summary of the results of the previous round is communicated to the participants.

Implementation of the experts' recommendations

During the 4th quarter of 1996, a specific course of training for clinicians was started. In accordance with the previously published guidelines for medical practice [5–7] an antiemetic prescription order form, which summarized the guidelines (Appendix 1), had to be used at the time of prescription and sent to the hospital pharmacy. After October 1996, no antiemetics were supplied without a completed antiemetic prescription order form.

Assessing the impact of the guidelines [8, 9]

To assess the impact of the guidelines, a 'before and after' study of the antiemetic drugs used in chemotherapy was performed at the Tenon Hospital, in 1995, 1997 and 1998, from March to August. During these three periods, all the consecutive in-patient units where chemotherapy was prescribed were enrolled in the study. Data were entered in a Newton palm-top computer (Apple), that easily fits into a lab coat pocket. The characteristics of this computer were as follows: 4Mb chip, 3 Mb extended life memory, and 32 bit-RISC processor. Special software was devised in collaboration with a software development company (MdEo, Puteaux, France). Scrolling menus were designed by the senior clinicians constituting the Tenon Working Group. Data on drug prescription, sex, age, and cancer sites were recorded at the patient's bedside. Each recorded item was checked before being downloaded into a microcomputer in the central biostatistics unit.

Drug utilization was classified as 'appropriate' when the guidelines were strictly applied. Patients were classified as 'overtreated', either when their regimen comprised higher doses than those recommended, or when a 5-HT₃ antagonist was prescribed but had not been recommended. Patients were classified as 'undertreated', either when a corticosteroid or 5-HT₃ receptor antagonist was not prescribed although it had been recommended, or when a 5-HT₃ receptor antagonist was not prescribed but had been recommended. Because prices were not stable during the study period, we based our study of cost savings on the prices prevailing in November 1998. Note that ondansetron and granisetron, the only 5-HT₃ receptor antagonists available in our institution, cost exactly the same.

Results

Points agreed on by the Delphi experts

The prescription form for antiemetogenic agents (Appendix 1) was drafted in accordance with the guidelines obtained from the Delphi experts (Appendix 2).

The points agreed on by these experts were the classification of emetogenic anticancer drugs into the three groups listed in Appendix 1, the medical indication for each group, the list of risk factors for nausea and vomiting, a definition of the failure of antiemetic treatment, and the efficacy and safety characteristics of antiemetic drugs.

Emetogenic potential Failure of the panel of outside experts to agree on the four group classification of emetogenic anticancer drugs proposed by the Tenon Working Group led to the adoption of a three group classification based on three therapeutic approaches (Appendix 1). In the administration of several emetogenic anticancer drugs to the same patient, the experts agreed to classify these drugs according to their strongest emetogenic potential. Eleven of the 14 experts agreed to include cisplatin in the highly emetogenic class, whatever its dosage.

Risk factors Five of the 14 experts did not agree, in the third round of discussions, to include a history of nausea and vomiting during pregnancy, the intravenous route of administration, or a day care setting. All the experts reached agreement on the risk factors listed in Appendices 1 and 2.

Definition of failure During the second round of Delphi consultations, the experts agreed to define the failure of antiemetic treatment as the occurrence of one or more attacks of nausea or vomiting during the first 24 h after chemotherapy drug ingestion.

5-HT₃ receptor antagonist receptor efficacy For the two 5-HT₃ receptor antagonists in use at the Tenon hospital, 12 of the 14 Delphi experts considered 3 mg granisetron equivalent to 8 mg ondansetron.

Drug safety The antiemetic agents listed in Appendix 1, including the above 5-HT₃ receptor antagonists, were

considered by all the experts to be well tolerated. They were aware of the association between high doses of phenothiazine and acute dyskinesia, but did not consider this a contraindication for phenothiazine administration. Three circumstances were considered as contraindications for the prescription of corticosteroids in cancer: diabetes, gastroduodenal ulcer, and a history of psychiatric disorders.

Patients

Pharmacists enrolled 174 consecutive in-patients receiving chemotherapy from March to August 1995, 166 from March to August 1997, and 163 from March to August 1998.

From March to August 1995, highly emetogenic anticancer drugs were prescribed for 125/174 patients (71%), moderately emetogenic anticancer drugs, for 29 patients (17%), weakly emetogenic anticancer drugs for 20 patients (12%).

From March to August 1997, highly emetogenic anticancer drugs were prescribed for 72/166 patients (43%), moderately emetogenic anticancer drugs, for 70 patients (42%) and weakly emetogenic anticancer drugs for 24 patients (14%).

From March to August 1998, highly emetogenic anticancer drugs were prescribed for 68/163 patients (42%), moderately emetogenic anticancer drugs, for 63 patients (39%) and weakly emetogenic anticancer drugs for 32 patients (19%).

Physician compliance before and after guideline implementation

Totally inappropriate use Before the Delphi panel's guidelines were implemented, inappropriate use of 5-HT₃ receptor antagonists was recorded for 123/174 patients

Table 1 Appropriateness of antiemetic prescription before and after Delphi guideline implementation.

	March to August 1995	March to August 1997	March to August 1998	Fisher's exact test probability
Totally inappropriate use of 5-HT ₃ receptor antagonists	123/174 70	36/166 22	45/163 28	* <i>P</i> < 0.0001 ** <i>P</i> < 0.0001
Undertreatment	74/174 (43%)	12/166 (7%)	13/163 (8%)	* <i>P</i> < 0.0001 ** <i>P</i> < 0.0001
Overtreatment	49/174 (28%)	24/166 (14%)	29/163 (18%)	* <i>P</i> = 0.003 ** <i>P</i> = 0.03

*March to August 1995 and March to August 1997.

**March to August 1995 and March to August 1998.

(70%). After guideline implementation, these figures dropped significantly ($P < 0.0001$, Fisher's exact test, Table 1) to 36/166 (22%) for March to August 1997, and to 45/163 (28%) for March to August 1998.

Undertreatment Before guideline implementation, 74/174 patients (43%) were 'undertreated' for the sole reason that 5-HT₃ receptor antagonists were not administered with corticosteroids although this had been recommended. After implementation, these figures dropped significantly ($P < 0.0001$, Fisher's exact test, Table 1): Thus, from March to August 1997, 12/166 patients (7%) were undertreated, and from March to August 1998, 13/163 (8%) because 5-HT₃ receptor antagonists were not administered with corticosteroids when this was recommended.

Overtreatment From March to August 1995, 49/174 patients (28%) were 'over treated'. These figures dropped significantly ($P < 0.05$ Fisher's exact test, Table 1) to 24/166 patients (14%) for March to August 1997, and to 29/163 (18%) for March to August 1998.

Cost saving study

As Figure 1 shows, a rapid but transient decrease in 5-HT₃ receptor antagonist delivery occurred between March and August 1995. By the end of the study

Figure 1 5-HT₃ receptor antagonist consumption (expressed in vials containing 8 mg ondansetron per vial or 3 mg granisetron) in the Tenon Hospital from the first quarter of 1994 to the third quarter of 1998. Before = before Delphi guideline implementation. Hawthorne effect: the positive effect on drug performance of a patient's inclusion in a research project. Abscissae: Time expressed in years (Y) and quarters (Q). — 5-HT₃ receptor antagonists, □ granisetron, △ ondansetron.

conducted before guideline implementation, i.e. by August 1995, the level of consumption had returned to its level at the beginning of the study, in March 1995. After the implementation of the Delphi experts' guidelines began in October 1996, 5-HT₃ receptor antagonist use diminished continuously in the hospital. Table 2 shows the annual figures, expressed as the number of 5-HT₃ receptor antagonist vials supplied, and their cost in French francs.

Discussion

Between 1995 and 1998, a rational procedure for monitoring the prescription of antiemetics was implemented in our 850-bed Paris hospital. This procedure is still in general use, with the agreement of hospital physicians. In 1995, a Working Group was initiated comprising senior physicians from the oncology, radiotherapy and respiratory departments, and a hospital pharmacist, in rather complex circumstances: the drug market was rapidly changing and pressure for cost containment was high. The Working Group implemented recommendations agreed on by an external group of experts in accordance with the Delphi technique, which can be used to determine the qualifications required for admission to further medical education in therapeutics [10]. This technique allowed physicians to take part in courses, to improve their knowledge and also to develop prescribing skills. An appropriate organization is in place to facilitate the process. It was essential to see that the physicians who will use the guidelines take part in the process of guideline development, to ensure their co-operation and support. Accordingly, a strategy for obtaining a consensus was built into the process, and clinical experience provided part of the basis for the guidelines recommended. Furthermore, physician compliance, for instance, with the recommendations to combine corticosteroids with 5-HT₃ receptor antagonists, is easier to obtain when strong evidence of beneficial results is available.

The Delphi technique enabled the experts to agree on the classification of anticancer drugs as strongly, moderately or weakly emetogenic. The pharmacological type of anticancer drugs is the most important factor in the onset of emesis. Several classifications have been published, most of them comprising 3–5 groups [11–13]; there are discrepancies between these classifications, because some anticancer drugs are considered to have high emetogenic potential in one classification and moderate in another. Some classifications take the dosage into account. No explicit methodology has been published for the application of these classifications, and there is no

Table 2 Cost saving during the drug utilization review process.

	Number of vials of 5-HT ₃ receptor antagonists	Cost (French francs*)	Decrease (%)
1994: before the drug utilization review	6.073	196.765	—
1995: review period	5.855	189.702	—3
1996: implementation of Delphi guidelines	5.308	171.979	—9
1997: 1 year after implementation	4.058	131.479	—24
1998: 2 years after implementation	3.625	117.450	—11

*The price per vial of 5-HT₃ receptor antagonist was the price prevailing in Dec, 1998, i.e. 32.4 French francs.

international agreement. This complexity lends itself to the use of the Delphi technique. The experts agreed on a three group classification defined above because it corresponded to the three practical therapeutic approaches the groups had in common: (i) administration of 5-HT₃ receptor antagonists by the i.v. route (8 mg day⁻¹ ondansetron or 3 mg day⁻¹ granisetron [14]; (ii) their administration by the oral route, and (iii) administration of non 5-HT₃ receptor antagonists. Although the efficacy of the combined use of corticosteroids and 5-HT₃ receptor antagonists has been established in the literature [15], the results of the study carried out here before guideline implementation highlighted the local under-prescription of corticosteroids. The Delphi group of experts agreed that it was safe for cancer patients to use corticosteroids for short periods. Locally, the recommendations for better use of corticosteroids led to a major change in therapeutic attitudes.

The Delphi process is recognized as one of the most valuable ways of determining the skills required of practising physicians [16]. Furthermore, it has been shown that physicians who are willing to participate in expert panels are representative of their colleagues [17]. The 14 external experts on our Delphi panel were chosen by the physicians in the Working Group of the Tenon hospital, according to subjective criteria (i.e. their reputation, and their involvement in the treatment of patients with cancer in French hospitals). Since the main objective of their recommendations for drug utilization was to provide acceptable guidelines, the most important criterion was that they should be recognized as experts by the clinicians. As the experts were asked to express their views in writing, by means of questionnaires, they did not need to meet, thus minimizing the negative effects of direct group interaction. Another advantage of this process is that Delphi panel members were unaware of each others' identities so no bias was introduced by conferring. The Delphi process relies on the general expertise and experience of leading members of the professions concerned.

Among the factors affecting the successful introduction of guidelines based on the experts' recommendations, Grimshaw and Russel showed that the best strategy was to implement an antiemetic prescription order form [17]. This form is now available throughout our hospital, but its validity is limited to 1 year. Once a year, the original Delphi panel recommendations are updated by the Working Group, and the updated recommendations are validated by the group of external experts in a single round of discussions.

As in any uncontrolled study, which is the major limitation of the present work, it is possible that factors other than those included in the guidelines defined here helped to reduce drug consumption. One effect of the drug utilization review, described elsewhere as the Hawthorne effect [7] (i.e. the beneficial effect on drug performance of patient inclusion in a research project) was indeed observed during the study conducted before guideline implementation. Although this effect is known to be transient, the 5-HT₃ receptor antagonist consumption measured in the study after guideline implementation remained at the lowest level ever observed in our hospital, probably as a result of the implementation of the expert panel's recommendations. All prescriptions that do not conform to the experts' recommendations are routinely reviewed by this panel. During the drug utilization review, no significant change was noted in hospital activity: thus, the number of patients admitted to the oncology department only increased by 13% between 1996 and 1997, and decreased by 7% between 1997 and 1998, and the duration of the hospital stay remained stable (6 days $\pm$ 1). Nevertheless, we cannot assert that the conditions of the patients admitted before guideline implementation was similar to the condition observed thereafter. In addition, 5-HT₃ receptor antagonists became more popular with physicians during the study period, their efficacy was better publicised, they caused no serious adverse effects, and their cost decreased. Between 1996 and the present time (April 1999), no new antiemetics have been introduced in our hospital, thus

ruling out one possible reason for changes in prescriptions. Oral forms of 5-HT₃ receptor antagonists were the only innovations during the study period, but they did not supplant the forms administered i.v. (for example, as from 1996, only one unit of oral 5-HT₃ receptor antagonists was supplied by the pharmacy for every 20 vials of the i.v. form). In our opinion, all these external factors would have increased the use of 5-HT₃ receptor antagonists if efficient guidelines for drug prescription had not been implemented. In other Paris hospitals also, the use of 5-HT₃ receptor antagonists decreased in 1996 and 1997, but only by 3.5%, compared with 24% in the Tenon Hospital. From 1997 to 1998, the use of 5-HT₃ receptor antagonists increased by 15% in the other Paris hospitals, but their consumption at Tenon decreased by 13%.

Conclusion

The study conducted before guideline implementation revealed many cases in which inappropriate drugs had been administered. Although it was not possible here to demonstrate a causal relationship between guidelines and changes in medical practice, it is very encouraging to note that the after implementation of guidelines in the Tenon Hospital, physician compliance with the panel's recommendations improved and was regular. Our study shows that when practitioners are involved in a dynamic process, which in this case included the Delphi technique, their compliance with the resulting guidelines is effective. However, the ultimate evaluation must involve outcome studies, to assess the impact of the guidelines on patient care.

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time limit of this sheet :

Paste the patient's label
here**Antiemetic prescription order form to be used in emesis
induced by chemotherapy (ChT) or radiotherapy (RT)**

(these drugs are recommended by the Tenon Hospital antiemetic working group)

Prescriber :

Ward :

Room No :

Signature :

High emetic potential ChT / /

dactinomycin
carmustine
chlormethine
cisplatin
cyclophosphamide >1g/m²/d
cytarabine
dacarbazine
lomustine
procarbazine
streptozocin

Moderate emetic potential ChT / /
High emetic potential RT / /

asparaginase
carboplatin
5-fluoro-uracil >1g/m²/d
cyclophosphamide ≤1g/m²/d
doxorubicin
epirubicin
fludarabine
fotemustine
ifosfamide
methotrexate
mitoxantrone
mitomycin
oxaliplatin
6-thioguanine
teniposide

Low emetic potential ChT / /

bleomycin
5-FU ≤1g/m²/j
docetaxel
etoposide
gemcitabine
hydroxycarbamide
paclitaxel
raltitrexed
thiotepa
topotecan
vinblastine
vincristine
vindesine
vinorelbine

a) right away check in appropriate box
- granisetron: 3mg IV / /
- ondansetron: 8mg IV / /
- and steroids / /
(dexamethasone: 20 mg or methylprednisolone: 120 mg)

b) in case of failure
- combine with a different class of antiemetic
(e.g. benzamide, phenothiazine, or benzodiazepine)
specify : / /
- or 2 vials of anti-5HT₃, i.e.
granisetron: 2x3mg IV / /
or ondansetron: 2x8mg IV / /
- and steroids / /
(dexamethasone: 20 mg or methylprednisolone: 120 mg)
c) for delayed vomiting after ChT or RT
- ondansetron: 2 tab 8mg / day / /

a) right away check in appropriate box
- granisetron: 1 tab 1mg 1 hr prior to ChT and 1 tab 12 h
thereafter / /
- or ondansetron: 1tab 8mg 2 hr prior to ChT / /
- if oral route is not possible, granisetron 3mg IV / /
or ondansetron: 8mg IV / /
- or metoclopramide / /
(5mg/kg/d: 2mg/kg/d in 15 minutes, followed by
3mg/kg/d during infusion of ChT)
- combined or not with steroids / /

b) in case of failure or for safety
- combine with a different class of antiemetic
(e.g. benzamide, phenothiazine, or benzodiazepine)
specify : / /
c) right away for RT
- ondansetron: 1tab 8mg 2 hr prior to RT / /

a) no antiemetic right away
b) in case of failure or right away if risk factors*
check in appropriate box
- granisetron: 1 tab 1mg 1 hr prior to ChT and 1 tab 12 h
thereafter / /
- or ondansetron: 1tab 8mg 2 hr prior to ChT / /
- or metoclopramide: 30 mg/d / /
- combined or not with steroids / /

*** risk factors** : when relevant, please check appropriate
item on the list identified by the Delphi expert group
- combination of 2 or more cytotoxic agents / /
- age < 50 yrs / /
- woman / /
- anxiety / /
- emesis experienced in previous cycles / /

Days of treatment (please circle)

emet/v.98.1/B/engl

Appendix 1 Prescription order form for antiemetics.

Appendix 2 Guidelines for the use of 5-HT₃ receptor antagonists in chemotherapy-induced acute nausea and vomiting

High emetic potential chemotherapy (ChT):

Right away: 3 mg granisetron i.v. or 8 mg ondansetron i.v. 15 min before ChT, and steroids.

In case of failure: combination of a different class of antiemetic, and steroids, or 16 mg ondansetron i.v. or 6 mg granisetron i.v., and steroids.

Moderate emetic potential chemotherapy:

Right away: 1 mg granisetron orally, 1 h before ChT and 12 h thereafter, or 8 mg ondansetron orally, 2 h before ChT, with or without steroids. If the oral route is not possible: 3 mg granisetron i.v. or 8 mg ondansetron

i.v., 15 min before ChT with or without steroids or a bolus of 2 mg kg⁻¹ day⁻¹ metoclopramide followed by 3 mg kg⁻¹ day⁻¹, with or without steroids.

In case of failure: combination of a different class of antiemetic, and steroids, or 16 mg ondansetron i.v. or 6 mg granisetron i.v., and steroids.

Low emetic potential chemotherapy:

Right away: no antiemetic

In case of risk factors†: 1 mg granisetron orally, 1 h before ChT and 12 h thereafter, or 8 mg ondansetron orally, 2 h before ChT, or 30 mg day⁻¹ metoclopramide.

† List of risk factors agreed on by the experts: a combination of two or more anticancer drugs with the same emetic potential, age < 50 years, female sex, anxiety, emesis experienced during previous ChT cycles.